rapamycin to inhibit both inflammation and fibrosis, rapamycin and its derivatives may hold promise as new additions to the armamentarium in our fights against chronic kidney fibrotic diseases.

REFERENCES

1. Eddy AA. Molecular basis of renal fibrosis. *Pediatr Nephrol* 2000; **15**: 290–301.
2. Sarbassov DD, Ali SM, Sabatini DM. Growing roles for the mTOR pathway. *Curr Opin Cell Biol* 2005; **17**: 596–603.
3. Guertin DA, Sabatini DM. An expanding role for mTOR in cancer. *Trends Mol Med* 2005; **11**: 353–361.
4. Fajadet J, Morice MC, Bode C *et al*. Maintenance of long-term clinical benefit with sirolimus-eluting coronary stents: three-year results of the RAVEL trial. *Circulation* 2005; **111**: 1040–1044.
5. Law BK. Rapamycin: an anti-cancer immunosuppressant? *Crit Rev Oncol Hematol* 2005; **56**: 47–60.
6. Pallet N, Thervet E, Le Corre D *et al*. Rapamycin inhibits human renal epithelial cell proliferation: effect on cyclin D3 mRNA expression and stability. *Kidney Int* 2005; **67**: 2422–2433.
7. Tao Y, Kim J, Schrier RW *et al*. Rapamycin markedly slows disease progression in a rat model of polycystic kidney disease. *J Am Soc Nephrol* 2005; **16**: 46–51.
8. Chen JK, Chen J, Neilson EG *et al*. Role of mammalian target of rapamycin signaling in compensatory renal hypertrophy. *J Am Soc Nephrol* 2005; **16**: 1384–1391.
9. Bonegio RG, Fuhro R, Wang Z *et al*. Rapamycin ameliorates proteinuria-associated tubulointerstitial inflammation and fibrosis in experimental membranous nephropathy. *J Am Soc Nephrol* 2005; **16**: 2063–2072.
10. Wu MJ, Wen MC, Chiu YT *et al*. Rapamycin attenuates unilateral ureteral obstruction-induced renal fibrosis. *Kidney Int* 2006; **69**: 2029–2036.
11. Liu Y. Epithelial to mesenchymal transition in renal fibrogenesis: pathologic significance, molecular mechanism, and therapeutic intervention. *J Am Soc Nephrol* 2004; **15**: 1–12.
12. Aguilera A, Aroeira LS, Ramirez-Huesca M *et al*. Effects of rapamycin on the epithelial-to-mesenchymal transition of human peritoneal mesothelial cells. *Int J Artif Organs* 2005; **28**: 164–169.
13. Shihab FS, Bennett WM, Yi H *et al*. Sirolimus increases transforming growth factor-β1 expression and potentiates chronic cyclosporine nephrotoxicity. *Kidney Int* 2004; **65**: 1262–1271.

see original article on page 2037

Tools to detect and modify sickle cell nephropathy

JI Scheinman[1]

Placement of the development of a sickle cell nephropathy in a time/event line is helped by better measures of glomerular filtration rate, tubular dysfunction, and proteinuria. Preventing or slowing the nephropathy can improve the outcome of this complication of the devastating sickle cell disease.

Kidney International (2006) **69**, 1927–1930. doi:10.1038/sj.ki.5000412

A major thrust in nephrology has been the development of guidelines for improving global outcomes of kidney disease (http://www.Doqi.org). Delaying kidney failure is especially important when the risk is higher, as in diabetes mellitus and sickle cell disease, which carry a risk of serious chronic kidney disease as high as 25%.[1] Far more than in other diseases, when kidney failure occurs in sickle cell disease, the treatment chosen by patient and physician is likely to be dialysis, a functionally and economically poorer choice than transplantation.[1]

As they report in the current issue, Voskaridou *et al.*[2] studied 87 subjects with sickle cell/β-thalassemia to learn whether renal damage and progressive kidney disease can be detected earlier by better measures of renal function (with cystatin-C levels greater than 0.96 mg per liter) and markers of tubular damage (with serum β_2-microglobulin levels greater than 1.8 mg per liter and urinary *N*-acetyl-β-D-glucosaminidase levels greater than 2 units per day), compared with creatinine (CR) clearance alone (less than 80 ml per minute per 1.73 m^2) or serum CR alone (greater than 99 μmol per liter, or 1.125 mg per deciliter). It is assumed that sickle cell/β-thalassemia, although generally a milder process than HbSS sickle cell disease, behaves similarly in the development of a chronic nephropathy. This study helps to place the sickle cell disease patient into an appropriate time/event line (Figure 1) leading to kidney failure.

It has been clear that young sickle cell disease patients have a high glomerular filtration rate (GFR), which decreases over time in many. This loss of renal function may not be apparent, as CR is usually low. Of the 87 sickle cell/β-thalassemia subjects, with an average age of 42.6 years, six had increased CR, 35 had decreased CR clearance, and 28 had increased cystatin-C.[2] Unfortunately, we do not know whether inhibition of tubular CR secretion might help correct the serum CR errors, nor how cystatin-C relates to true (iothalamate) GFR in this population, as they diverge in several contexts. If serum CR were to be used for GFR, sickle cell disease patients with diminished GFR would be erroneously assigned to stage 0 of kidney disease (http://www.Doqi.org) and be presumed to require attention more appropriate for later stages.

Beneath these errors in the estimation of GFR in sickle cell disease patients lie remarkable physiologic alterations. Nearly 30 years ago, Statius van Eps, de Jong, and colleagues proposed that distinctive renal physiologic derangements in sickle cell disease might lead to a chronic glomerulosclerosis, as they later summarized.[3] Under favorable conditions, sickling causes vascular sludging, occlusion, and even infarction. In the kidney, the medullary area provides those conditions and, over time, develops a form of renal papillary necrosis. Although usually asymptomatic, renal papillary necrosis may be detectable

[1]*University of Kansas Medical Center, Department of Pediatrics, Division of Nephrology, Kansas City, Kansas, USA.*
Correspondence: *JI Scheinman, University of Kansas Medical Center, 3901 Rainbow Boulevard, Room G-019, Miller Building, Kansas City, Kansas 66160-7330, USA.*
E-mail: jscheinman@kumc.edu

radiologically in as many as two-thirds of patients. It was proposed that renal papillary necrosis elicits a prostaglandin (PG)-mediated vasodilatory response that may explain increased GFR, proximal tubular hyperfunction, and proteinuria, with the ultimate consequence of glomerular sclerosis. More recent studies have fine-tuned these hypotheses, but practical measures have not emerged to predict and prevent a chronic focal segmental glomerular sclerotic sickle cell nephropathy.

What leads from sickling to glomerular hypertrophy, renal papillary necrosis, proteinuria, focal segmental glomerular sclerosis, and kidney failure? The PG response to renal sickling may not only serve the kidney: PGE_2 also stimulates HbF in sickle cell blood-forming colonies *in vitro*, which would decrease the tendency toward red blood cell sickling.

Features of renal papillary necrosis in sickle cell disease were explored in a bromoethylamine model of renal papillary necrosis in mice and were compared with features of equivalent partial physical kidney ablation.[4] Both models resulted in the same serum CR levels, similar total (counted) nephron numbers, similar (measured) superficial single-nephron GFRs, and similarly increased glomerular pressure. With the ablation model, blood pressure, urine volume, and proteinuria were greater. Overall kidney weight was increased in the renal papillary necrosis group, perhaps reflecting glomerular hypertrophy. Hypertrophy is found in focal segmental glomerular sclerosis with disparate causes, including hyperlipidemic hypoinsulinemic glycogen storage disease.[5] The hypertrophy of cyanotic congenital heart disease is more comparable to that of sickle cell disease. In sickle cell disease, glomerular hypertrophy appears to be maximal and universal[6] but is potentially reversible.

The differences between these models of kidney damage should be explainable: Within functioning nephrons (not necessarily in those micropunctured for single-nephron GFR), renal papillary necrosis may result in a higher GFR with an increased ultrafiltration coefficient (that is, more filtration for the same pressure) because of greater glomerular hypertrophy. Ablation, not selectively destroying deep nephrons, could allow greater pressure and resulting proteinuria in that deep area. The equivalent serum CR in both models, despite the smaller number of functioning nephrons that is seen in renal papillary necrosis, could in part result from the greater CR secretion in renal papillary necrosis. As a human parallel, in patients with early sickle cell disease with elevated inulin clearance and normal CR, the ultrafiltration coefficient is increased.[7] The ablation model may be influenced more by the effects of angiotensin, which upregulates autoregulation — that is, the increase in glomerular resistance in response to increased perfusion pressure. Autoregulation is opposed by relaxation induced by nitric oxide and PG. In other models, angiotensin inhibition allows the relaxation effect of PG and nitric oxide, allowing the glomerulus to experience greater perfusion, and thus increased GFR. In still another context, experimental cirrhosis with ascites, PG is involved in maintaining GFR. In this situation, as in sickle cell disease, PG inhibition decreases GFR, whereas in normal subjects it does not affect GFR. A potentially valuable area of investigation may be the physiologic role of other prostanoids, such as PGI_2, in glomerular perfusion: There is evidence that a PGI_2 analogue (beraprost) allows, with partial nephron ablation, maintenance of GFR without glomerular hypertension.

The connection between sickling and the renal papillary necrosis of sickle cell disease would appear to be straightforward but for the elaborate endogenous mechanisms that appear to be important in dealing with defective perfusion. A prominent example is the heat shock system, represented by HSP70, which has been increased systemically in vaso-occlusive diseases, and locally in the renal medulla. HSP70 might be stimulated by PG, as cyclooxygenase-2 inhibition decreases HSP70 (in dehydrated rats), making the cells more susceptible to papillary apoptosis.

While investigating possible 'ischemic preconditioning' (resistance to repeated ischemic damage) in a transgenic SS mouse model, Nath *et al.* instead found greater susceptibility to ischemia, with increased vascular congestion, an increase in the inflammatory marker serum amyloid-P component (SAP, a homologue of C-reactive protein in humans), and increased caspase-3 (evidence of an increased cell-death pathway).[8] Their previous work investigated the status of oxidant stress in the SS model, because of the exposure of the renal medulla, after sickling with hemolysis, to large amounts of heme, a lipophilic pro-oxidant. The kidney then responded to this oxidant stress with the induction of heme oxygenase. These observations emphasize the susceptibility of the inner kidney to damage from sickling, which include renal papillary necrosis.

Proteinuria

Recently, the efforts to improve outcomes of kidney disease have included the targeting of proteinuria (http://www.Doqi.org) as a predictor and possible preventable cause of decreasing kidney function. Urine albumin excretion of more than 30 mg per day in the general population is predictive of the risk of de novo development of impaired GFR (less than 60) in 4 years.

Voskaridou *et al.*[2] found abnormal proteinuria in 30% of subjects, correlated with increased CR and cystatin-C (personal communication), as well as measures of tubular damage (β_2-microglobulin greater than 1.8 mg per liter) and *N*-acetyl-β-D-glucosamine. How many more of these subjects might have had microalbuminuria (by radioimmunoassay) when as many as 40% of patients with sickle cell disease have been shown to have it? Even more may be detected by a high-pressure liquid chromatography method that detects non-immunoreactive albumin fragments, which could reflect early perturbed tubular protein processing.

The decrease in proteinuria shown by the sickle cell/β-thalassemia subjects in response to short-term angiotensin-converting enzyme inhibition[2] is consistent with our[9] and others' findings. The same effect has been seen on microalbuminuria in sickle cell disease. In the current study,[2] angiotensin-converting enzyme inhibition also lowered *N*-acetyl-β-D-glucosamine, which was used as an indicator of tubular damage.

Average age (y)	Clinical observation	Process	Modifier	Therapeutic effort
	Harms ↓ Helps ↑	Harms ↓ Helps ↑	Aggravates ↓ Improves ↑	Inhibits ↓ Improves ↑
1	Anemia ↓	Sickling ↓	High HbF ↑	Hypertransfusion ↑
	Pain ↓			Hydroxyurea ↑
			Chg β-globin ↑	β-globin gene Rx ↑
			Incr. BbA ↑	Bone marrow transplant ↑
5	GFR ↑ SCr. ↓	Medullary congestion ↓	Incr. adhesion ↓	
	Hematuria ↓		High oxygen ↓	
		Hyperperfusion ↑	High COX-1 ↑	ACEI
		Hypertrophy-EGF ↑	Hypoxia ↓	Somatostatin analogue ↑
		Papillary necrosis ↓	High NO ↑	
			High caspase-3 ↑	
			High HSP70 ↑	
			Incr. COX-2 ↑	
10			High CRP ↓	
			High HO-1 ↑	
		Hyperfiltration ↑	Incr. AII ↓	ACEI ARB ↑
			High PGI_2 ↑	PGI_2 analogue ↑
			High HSP70 ↑	
15	High microalbuminuria ↔	Hyperperfusion ↓		ACEI ↑
20	High NAG ↑	Tubular function ↓		ACEI ↑
20	High β_2-M ↑	Tubular function ↓		
30	High proteinuria ↑	Glomerular Htx ↓		ACEI ↑
30	NI GFR	FSGS ↓		
35	Low GFR ↓			
35	Incr. Cys-C ↓			
40	Low Cr Cl ↓			
50	High Cr ↓			

Figure 1 | Time and event line for the development of sickle cell nephropathy. Average ages of onset are paired with clinical or laboratory markers underlying processes, endogenous physiologic modifiers and therapeutic possibilities. COX, cyclooxygenase; Cys-C, cystatin-C; GFR, glomerular filtration rate. Sickle cell illustration by Katie Ris.

Considerable experimental and observational data implicate the physiologic changes, and the accompanying albuminuria and proteinuria, as facilitators, if not the actual causes, of the development of focal segmental glomerular sclerosis. The causes of microalbuminuria and proteinuria are still unclear and are beyond this discussion.

Therapy

What avenues of prevention or therapy are suggested by clarification of the elements and time/event lines of development of a sickle nephropathy (Figure 1)?

Prevention of sickling or hemolysis, of course, should ideally interrupt the cascade at the beginning[10] and is currently being explored with bone marrow transplantation and clinical trials of β-globin gene therapy (begun in β-thalassemia). The effects of changing the balance of hemoglobins, by favoring HbF with hydroxyurea, have been extensively tested.[10] This approach is directed toward providing a lesser proportion of HbS, as does a protocol of hypertransfusion (with HbAA cells). Blocking adhesion of sickling cells to the endothelium would allow susceptible cells to leave the vulnerable environment before sickling and obstruction occur. The response of the kidney to medullary congestion and hypoxia may be modified by antioxidants, prostacyclin analogues, and angiotensin-converting enzyme inhibition. If glomerular hypertrophy itself promotes focal segmental glomerular sclerosis, it may be inhibited by somatostatin analogues. Glomerular hypertension can be reduced by angiotensin-converting enzyme inhibition and angiotensin receptor blockers; this reduction decreases proteinuria, which itself may be pathogenic. The many other factors that favor the progression of focal segmental glomerular sclerosis in other contexts, such as hyperlipidemia, protein loading, and salt intake, can further be modified. A comprehensive approach to a dangerous process in a vulnerable population requires identifying a patient's position in the time/event line of the disease. Voskaridou *et al.*[2] have provided another tool for this purpose.

REFERENCES

1. Scheinman JI. Sickle cell nephropathy. In: Avner ED Harmon WE, Niaudef P (ed). *Pediatric Nephrology*. Lippincott Williams & Wilkins: Philadelphia, 2004, pp 917–930.
2. Voskaridou E, Terpos E, Michail S *et al.* Early markers of renal dysfunction in patients with

sickle cell/β-thalassemia. *Kidney Int* 2006; **69**: 2037–2042.
3. de Jong PE, Statius van Eps LW. Sickle cell nephropathy: new insights into its pathophysiology. *Kidney Int* 1985; **27**: 711–717.
4. Rosenberg ME, Hostetter TH. Comparison of residual glomerular function in experimental papillary necrosis and renal infarction. *Am J Kidney Dis* 1990; **16**: 118–125.
5. Chen YT, Scheinman JI, Park HK *et al.* Amelioration of proximal renal tubular dysfunction in Type 1 glycogen storage disease with dietary therapy. *N Eng J Med* 1990; **323**: 590–593.
6. Bhathena DB, Sondheimer JH. The glomerulopathy of homozygous sickle hemoglobin (SS) disease: morphology and pathogenesis. *J Am Soc Nephrol* 1991; **1**: 1241–1252.
7. Schmitt F, Martinez F, Brillet G *et al.* Early glomerular dysfunction in patients with sickle cell anemia. *Am J Kidney Dis* 1998; **32**: 208–214.
8. Nath KA, Grande JP, Croatt AJ *et al.* Transgenic sickle mice are markedly sensitive to renal ischemia-reperfusion injury. *Am J Pathol* 2005; **166**: 963–972.
9. Falk RJ, Scheinman JI, Phillips G *et al.* Prevalence and pathologic features of sickle cell nephropathy and response to inhibition of angiotensin-converting enzyme. *N Engl J Med* 1992; **326**: 910–915.
10. Steinberg MH. Predicting clinical severity in sickle cell anaemia. *Br J Haematol* 2005; **129**: 465–481.

see original article on page 2043

Is there an increased long-term risk of hypertension and renal impairment after Puumala virus-induced nephropathy?

B Rippe[1]

Nephropathia epidemica (NE) is a mild form of hemorrhagic fever with renal syndrome, assumed to have a favorable prognosis. NE patients who manifested a higher glomerular filtration rate and mean systolic blood pressure, and more proteinuria, versus controls at 5 years of follow-up demonstrated no major abnormalities after 10 years. Antihypertensive treatment was, however, more common. Could NE predispose some patients to develop hypertension after all?

Kidney International (2006) **69**, 1930–1931. doi:10.1038/sj.ki.5000320

Puumala (PUU) virus-induced nephropathy in the form of NE occurs in northern parts of Scandinavia, Finland, and Russia, and in parts of Central and Western Europe. The virus is a member of the genus *Hantavirus* in the Bunyaviridae family, and its natural host is the bank vole (*Clethrionomys glareolus*). Over the past decades, hantavirus infection has attained an increased interest, and a review on the topic was recently published.[1]

[1]*Department of Nephrology, University Hospital of Lund, Lund, Sweden.*
Correspondence: *B Rippe, Department of Nephrology, University Hospital of Lund, S-211 85 Lund, Sweden.*
E-mail: Bengt.Rippe@med.lu.se

Nephropathia epidemica (NE) is characterized by sudden onset with high fever, headache, backache, and abdominal pain and transient early thrombocytopenia, not infrequently in conjunction with conjunctival hemorrhages, palatine petechiae, and truncal petechial rash. The hemorrhages are accompanied by oliguria, proteinuria, and hematuria. Within 3 days the rash disappears and the patient develops polyuria. The typical renal histopathologic lesion is acute tubulointerstitial nephritis. Proteinuria is most commonly due to a loss of albumin, reflecting glomerular injury, but concomitant tubular proteinuria reflected by increasing excretion of protein HC (α_1-microglobulin) and β_2-microglobulin indicates that tubular injury also contributes to the proteinuria. Severe courses of NE with acute renal failure and lethal outcome are very rare (<1%). The convalescent phase usually lasts from 3 weeks to 3 months.

The pathophysiology of hantavirus infection derives from the virus' replication in macrophages and vascular endothelial cells, especially those in the lung and in the kidney, resulting in severely increased endothelial permeability. The main structural protein of the virus is the nucleocapsid protein. For pathogenic hantaviruses, the entry into host cells occurs by attachment to $\alpha_v\beta_3$ integrin on the cellular surface and subsequent endocytosis, whereby nucleocapsids are released into the cytoplasm. Crucial in the pathophysiology of hantavirus infection is the increased endothelial permeability induced by various cytokines/chemokines (tumor necrosis factor-α, interferon-γ, interleukin-6, and others). Also, the interaction with $\alpha_v\beta_3$ integrin molecules seems to result in defective endothelial permeability regulation.[2]

The long-term prognosis of NE is usually considered favorable. A series of 46 patients in Tampere, who had gone through NE 3–7 years previously, manifested a higher glomerular filtration rate and filtration fraction, more proteinuria, and a higher mean ambulatory systolic blood pressure as compared with 38 healthy seronegative control subjects.[3] In a study conducted after the Korean War, two of 13 patients with previous hemorrhagic fever with renal syndrome had hypertensive vascular disease.[4] Furthermore, in a large epidemiological survey from Baltimore, there was an association between a previous infection with rat-borne Seoul-like hantavirus and an increased risk of hypertensive renal disease.[5] By contrast, a Swedish study did not demonstrate any differences in office blood pressure between 110 PUU virus antibody-positive and 682 antibody-negative individuals.[6] However, in this material there was a significant correlation between PUU antibody positivity and hypertension in individuals older than 60 years of age.

A 10-year follow-up study of the Tampere material[3] represents the hitherto largest prospective clinical follow-up trial